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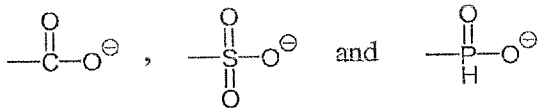
(54) Title: METHOD OF TREATMENT



(57) Abstract: The present invention relates to a method of preventing or treating hyperglycemia in a human or animal subject, the method comprising administering to the subject a therapeutically effective amount of a compound selected from the group consisting of: (a) a betaine compound having a positively-charged group selected from group consisting of a quaternary ammonium group, a quaternary phosphonium group and a tertiary sulfonium group, and a negatively-charged group selected from the group consisting of formula (I): (b) 2 trimethylamino-6 ketoheptanoate, (c) proline, (d) N methyl-L proline, *trans* 4 hydroxy-N methyl-L proline, (e) *cis* 3 hydroxy-N-methyl-L-proline, and (f) choline.

METHOD OF TREATMENT

FIELD OF THE INVENTION

This invention relates to a method of preventing or treating hyperglycemia in human or animal subjects.

BACKGROUND

Diabetes mellitus (hereinafter referred to as "diabetes") is a chronic disease caused by inherited and/or acquired deficiency in the production of insulin by the pancreas, or by the ineffectiveness of the insulin produced (impaired glucose tolerance). Diabetes results in above normal concentrations of glucose in the blood (hyperglycemia), which, in turn, damages many of the body's systems, in particular the blood vessels, eyes and nerves.

There are 3 forms of diabetes:

- **Type 1 diabetes**. Type 1 diabetes (formerly known as "insulin-dependent diabetes") results from the failure of the pancreas to produce insulin which is essential for survival. This form of diabetes develops most frequently in children and adolescents, but is being increasingly noted later in life.
- **Type 2 diabetes**. Type 2 diabetes (formerly known as "non-insulin-dependent diabetes") results from the body's inability to respond properly to the action of insulin produced by the pancreas. Type 2 diabetes is more common than type 1 diabetes and accounts for about 90% of all diabetes cases worldwide. It occurs most frequently in adults, but is being noted increasingly in adolescents as well.
- **Diabetes in pregnancy**. Diabetes in pregnancy (gestational diabetes) may give rise to several adverse outcomes, including congenital malformations, increased birth weight and an elevated risk of perinatal mortality.

Recently compiled data by the World Health Organisation (WHO) shows that at least 171 million people worldwide suffer from diabetes, and 90% of these patients suffer from type 2 diabetes. It is expected that the number of people with diabetes will increase over the next few decades due to increasing population in developing

countries, ageing of populations, and increasing incidence of unhealthy diets, obesity and sedentary lifestyles.

Type 1 diabetes is usually, but not only, treated with the injection of insulin. Various forms of treatment exist for sufferers of type 2 diabetes, including the administration of antidiabetic drugs, such as biguanides, sulfonylureas, alpha-glucosidase inhibitors, meglitinides and thiazolidinediones.

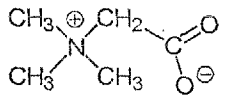
Metformin is the only currently commercially available biguanide antidiabetic drug. Although Metformin has been available throughout Europe for over 40 years, its mechanism of action has been elucidated only in recent years. Metformin decreases blood-glucose levels by reducing hepatic glucose output and enhancing insulin sensitivity in hepatic and peripheral tissues (Sirtori CR, and Pasik C, "Re-evaluation of a biguanide, metformin: mechanism of action and tolerability". *Pharmacol Res.* **30**:187-228 (1994)).

It would be advantageous to provide alternative methods of preventing or treating hyperglycemia in a human or animal subject. By preventing or treating hyperglycemia in a subject, the adverse effects of diabetes can be delayed or prevented.

Obesity is growing at an epidemic proportion in the developed nations. Obesity is a risk factor for conditions such as type 2 diabetes, cardiovascular disease and stroke. Recent statistics by the Australasian Society for the Study of Obesity show that 67% of men and 52% of women are overweight or obese in Australia. About 1.5 million Australians under the age of 18 years are also overweight or obese.

According to WHO, an estimated 17 million people worldwide die from cardiovascular diseases, particularly heart attacks and strokes, every year. Cardiovascular diseases contribute to about a third of deaths in the world. By 2010, it is expected that cardiovascular diseases will be the major cause of deaths in the world. High blood-lipid (lipid) levels (referred to as hyperlipidemia) leading to atherosclerosis results in cardiovascular diseases.

Glycine betaine (also known as N,N,N-trimethylammonioacetate, N-trimethylglycine, lycine and oxyneurine) is a betaine compound and is a natural component of several food grains and is produced as a by-product of the sugar beet industry in Finland and USA. It has been estimated that humans eat about 2 g of glycine betaine per day through diet. Glycine betaine has the following chemical structure:



Glycine betaine is used to treat homocystinuria by lowering levels of homocystine. Homocystinuria is a genetic condition whereby sufferers are unable to metabolise homocystine. Inability to metabolise homocystine leads to mental retardation, lack of growth, and other health problems. Glycine betaine has been known to correct metabolic abnormalities responsible for homocystinuria.

Glycine betaine has been shown to be a promising agent for the treatment of ethanol-induced fatty liver and non-alcoholic fatty liver. Glycine betaine is also considered to be a nutrient that plays an important role in the health of the cardiovascular system, and may help protect against fatty deposits in the liver caused by poorly controlled diabetes.

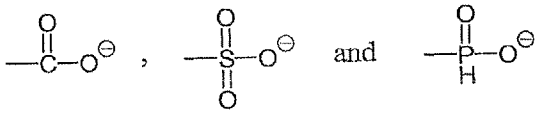
WO 00/51596 describes the use of glycine betaine to eliminate physiopathological vascular diseases. This document describes that glycine betaine shows curative and preventive effects in the pathogenesis of thromboembolic and hemostatic diseases of arterial or venous origin. Glycine betaine inhibits the formation of thrombi and also the proliferation of thrombi by eliminating them. This document also describes that glycine betaine may also be used as an anticoagulant for blood preservation.

WO 95/15750 describes a method of reducing the likelihood of heart attacks strokes or peripheral vascular diseases in patients by administering vitamin B6 together with at least one of glycine betaine, choline and lecithin.

SUMMARY OF THE INVENTION

In a first aspect, the present invention provides a method of preventing or treating hyperglycemia in a human or animal subject, the method comprising administering to the subject a therapeutically effective amount of a compound selected from the group consisting of:

(a) a betaine compound having a positively-charged group selected from group consisting of a quaternary ammonium group, a quaternary phosphonium group and a tertiary sulfonium group, and a negatively-charged group selected from the group consisting of:



(b) 2-trimethylamino-6-ketoheptanoate,

(c) proline,

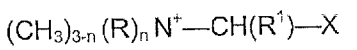
(d) N-methyl-L-proline, *trans*-4-hydroxy-N-methyl-L-proline,

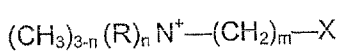
(e) *cis*-3-hydroxy-N-methyl-L-proline, and

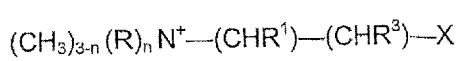
(f) choline.

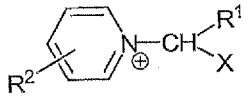
Typically, when the compound is a betaine compound, the positively-charged group in the betaine compound is a quaternary ammonium group or a tertiary sulfonium group.

In some embodiments, the compound is a betaine compound selected from the group consisting of:

 (I)

 (Ia)

 (Ib)



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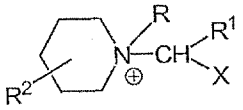

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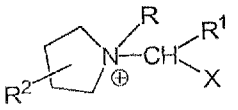

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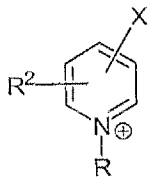

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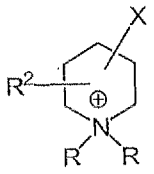

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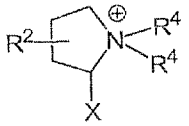

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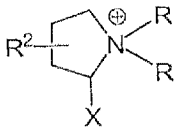


(VIIa)

wherein n is 0, 1 or 2;

m is 1 or 2;

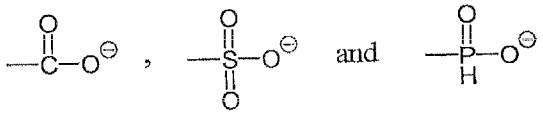
R is selected from the group consisting of optionally substituted alkyl and optionally substituted aryl groups;

R^1 and R^3 are independently selected from the group consisting of H, optionally substituted alkyl groups, carboxyl and side chains of amino acids;

R^2 is selected from the group consisting of OH, halo, optionally substituted alkyl groups, NH_2 and electrophilic groups;

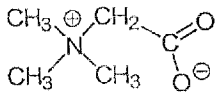
R^4 is an optionally substituted alkyl group; and

X is selected from the group consisting of



In some embodiments, the compound is selected from the group consisting of: glycine betaine, β-alaninebetaine, 2-trimethylamino-6-ketoheptanoate, prolinebetaine, proline, N-methyl-L-proline, *trans*-4-hydroxy-N-methyl-L-proline, *cis*-3-hydroxy-N-methyl-L-proline, (-)-4-hydroxy prolinebetaine, (+)-4-hydroxy prolinebetaine, 3-hydroxyprolinebetaine, histidinebetaine, tryptophanbetaine, 2-mercaptohistidinebetaine, pipecolatebetaine, nicotinic acid betaine, 3-dimethylsulfoniopropionate (DMSP), choline-O-sulfate , choline and $(CH_3)_3P^+CH_2S(=O)_2O^-$.

In a preferred embodiment, the compound is glycine betaine having the following formula:

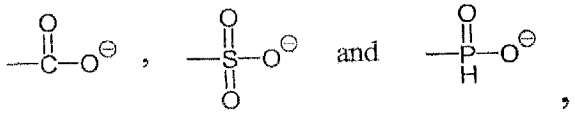


In some embodiments, the therapeutically effective dose of the compound is more than 20 mg/kg body weight per day, e.g. from about 20 mg/kg to 400 mg/kg body weight per day. In some embodiments, the dose administered is, for example, from about 100 to

400 mg/kg body weight, or about 200 to 400 mg/kg body weight. For an adult human subject, more than 1,000 mg per day may be administered to the subject, e.g. about 2,000 to 30,000 mg per day. The total daily dose of the compound may be administered to the subject in one dose or in divided doses during the day.

In a second aspect, the present invention provides the use of a compound selected from the group consisting of:

(a) a betaine compound having a positively-charged group selected from group consisting of a quaternary ammonium group, a quaternary phosphonium group and a tertiary sulfonium group, and a negatively-charged group selected from the group consisting of:



,

(b) 2-trimethylamino-6-ketoheptanoate,

(c) proline,

(d) N-methyl-L-proline, *trans*-4-hydroxy-N-methyl-L-proline,

(e) *cis*-3-hydroxy-N-methyl-L-proline, and

(f) choline,

in the manufacture of a medicament for preventing or treating hyperglycemia.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows graphs of feed intake over time for (A) male mice and (B) female mice fed feed supplemented with 0% w/w, 0.25% w/w, 0.5% w/w or 1.0% w/w glycine betaine (the values at 0 weeks are an average of all the mice allocated to all four feeds);

Figure 2 shows graphs of body weight over time for (A) male mice and (B) female mice fed feed supplemented with 0% w/w, 0.25% w/w, 0.5% w/w or 1.0% w/w glycine betaine (the values at 0 weeks are an average of all the mice allocated to all four feeds); and

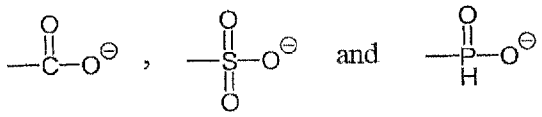
Figure 3 shows graphs of fasting blood-glucose levels over time for (A) male mice and (B) female mice fed feed supplemented with 0% w/w, 0.25% w/w, 0.5% w/w or 1.0% w/w glycine betaine (the values at 0 weeks are an average of all the mice allocated to all four feeds).

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Betaine compounds are a class of weakly basic substances which resemble glycine betaine. Betaine compounds are intramolecular salts (zwitterions). Betaine compounds are typically zwitterionic compounds derived from amino acids and contain a quaternary ammonium group. However, betaine compounds also include zwitterionic compounds containing tertiary sulfonium groups and quaternary phosphonium groups.

As used herein, a reference to a "compound of the invention" means a compound selected from the group consisting of:

(a) a betaine compound having a positively-charged group selected from group consisting of a quaternary ammonium group, a quaternary phosphonium group and a tertiary sulfonium group, and a negatively-charged group selected from the group consisting of:



(b) 2-trimethylamino-6-ketoheptanoate,

(c) proline,

(d) N-methyl-L-proline, *trans*-4-hydroxy-N-methyl-L-proline,

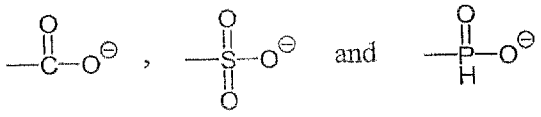
(e) *cis*-3-hydroxy-N-methyl-L-proline, and

(f) choline.

The present inventor has surprisingly found that the compounds of the invention are effective in the treatment of hyperglycemia, i.e. the compounds of the invention reduce blood-glucose levels in subjects having hyperglycemia. The present inventor has also found that the compounds of the invention can prevent the onset of hyperglycemia in subjects at risk of developing hyperglycemia. The present inventor has also found that the compounds of the invention are effective in enhancing the action of antihyperlipidemic agents to lower blood-lipid levels.

By preventing or treating hyperglycemia in a subject, the adverse effects of diabetes can be delayed or prevented.

The betaine compound may be any betaine compound having a positively-charged group selected from group consisting of a quaternary ammonium group, a quaternary phosphonium group and a tertiary sulfonium group, and a negatively-charged group selected from the group consisting of:

 and .

Typically, the positively-charged group in the betaine compound is a quaternary ammonium group or a tertiary sulfonium group. In some embodiments, the positively-charged group in the betaine compound is a quaternary ammonium group.

Typically, the positively-charged group and the negatively-charged group in the betaine compound are linked by one or more optionally substituted alkyl groups, typically a C_1-C_3 alkyl group such as methyl. The alkyl group may, for example, have one or more substituents selected from the group consisting of hydroxy, halo, alkyl, carboxyl, carbonyl, and side chains of amino acids. In some embodiments, the positively-charged group may form part of a cyclic group that may be saturated or unsaturated and may be optionally substituted, with the negatively-charged group bound to the cyclic group.

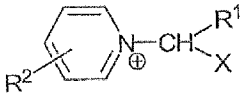
Suitable side chains of amino acids include, for example, side chains of the following amino acids: alanine, valine, leucine, isoleucine, aspartic acid, glutamine, serine, threonine, lysine, arginine, histidine, glutamic acid, cysteine, methionine, asparagine, tryptophan, tyrosine, phenylalanine and proline.

For example, the betaine compound may be selected from the following formulas I to VIIa:

$(CH_3)_{3-n}(R)_n N^+—CH(R^1)—X$ (I)

$(CH_3)_{3-n}(R)_n N^+—(CH_2)_m—X$ (Ia)

$(CH_3)_{3-n}(R)_n N^+—(CHR^1)—(CHR^3)—X$ (Ib)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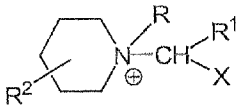
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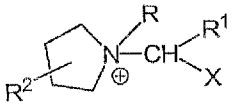
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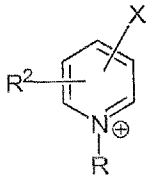
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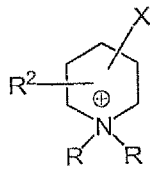

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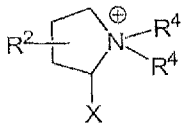

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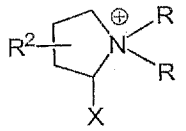


(VIIa)

wherein n is 0, 1 or 2;

m is 1 or 2;

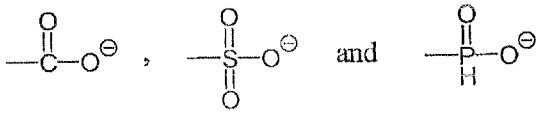
R is selected from the group consisting of optionally substituted alkyl (e.g. a C_1-C_5 alkyl group) and optionally substituted aryl (e.g. a C_6-C_{10} aryl group) groups;

R^1 and R^3 are independently selected from the group consisting of H, optionally substituted alkyl groups (e.g. a C_1-C_5 alkyl group), carboxyl and side chains of amino acids;

R^2 is selected from the group consisting of OH, halo, optionally substituted alkyl groups (e.g. a C_1-C_5 alkyl group), NH_2 and electrophilic groups;

R^4 is an optionally substituted alkyl group (e.g. a C_1-C_5 alkyl group); and

X is selected from the group consisting of



Typically, R^2 is selected from the group consisting of OH, halo, optionally substituted alkyl groups (e.g. a C_1-C_5 alkyl group) and NH_2.

The term "alkyl" denotes straight chain, branched or cyclic alkyl. Examples of straight chain and branched alkyl include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, amyl, isoamyl, sec-amyl, 1,2-dimethylpropyl, 1,1-dimethylpropyl, hexyl, 4-methylpentyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 1,2,2-trimethylpropyl, 1,1,2-trimethylpropyl, heptyl, 5-methylbexyl, 1-methylhexyl, 2,2-dimethypentyl, 3,3-dimethylpentyl, 4,4-dimethylpentyl, 1,2-dimethylpentyl, 1,3-dimethylpentyl, 1,4-dimethylpentyl, 1,2,3-trimethylbutyl, 1,1,2-trimethylbutyl, 1,1,3-trimethylbutyl, octyl, 6-methylheptyl, 1-methylheptyl, 1,1,3,3-tetramethylbutyl, nonyl, 1-, 2-, 3-, 4-, 5-, 6- or 7-methyloctyl, 1-, 2-, 3-, 4- or 5-ethylheptyl, 1-, 2- or 3-propylhexyl, decyl, 1-, 2-, 3-, 4-, 5-, 6-, 7- and 8-methylnonyl, 1-, 2-, 3-, 4-, 5- or 6-ethyloctyl, 1-, 2-, 3- or 4-propylheptyl, undecyl 1-, 2-, 3-, 4-, 5-, 6-, 7-, 8- or 9-methyldecyl, 1-, 2-, 3-, 4-, 5-, 6- or 7-ethylnonyl, 1-, 2-, 3-, 4- or 5-propyloctyl, 1-, 2- or 3-butylheptyl, 1-pentylhexyl, dodecyl, 1-, 2-, 3-, 4-, 5-, 6-, 7-, 8-, 9- or 10-methylundecyl, 1-, 2-, 3-, 4-, 5-, 6-, 7- or 8-ethyldecyl, 1-, 2-, 3-, 4-, 5- or 6-propylnonyl, 1-, 2-, 3- or 4-butyloctyl, 1-2 pentylheptyl and the like.

Examples of cyclic alkyl include mono- or polycyclic alkyl groups such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl and the like.

The term "aryl" denotes single, polynuclear, conjugated and fused residues of aromatic hydrocarbons or aromatic heterocyclic ring systems. Examples of aryl include phenyl, biphenyl, terphenyl, quaterphenyl, phenoxyphenyl, naphthyl, tetrahydronaphthyl, anthracenyl, dihydroanthracenyl, benzanthracenyl, dibenzanthracenyl, phenanthrenyl, fluorenyl, pyrenyl, indenyl, azulenyl, chrysenyl, pyridyl, 4-phenylpyridyl, 3-phenylpyridyl, thienyl, furyl, pyrryl, pyrrolyl, furanyl, imadazolyl, pyrrolydinyl, pyridinyl, piperidinyl, indolyl, pyridazinyl, pyrazolyl, pyrazinyl, thiazolyl, pyrimidinyl, quinolinyl, isoquinolinyl, benzofuranyl, benzothienyl, purinyl, quinazolinyl, phenazinyl, acridinyl, benzoxazolyl, benzothiazolyl and the like. The aromatic heterocyclic ring system may contain 1 to 4 heteroatoms independently selected from N, O and S.

The expression "optionally substituted" means that a group may or may not be further substituted with one or more groups selected from alkyl, alkenyl, alkynyl, aryl, halo, haloalkyl, haloalkenyl, haloalkynyl, haloaryl, hydroxy, alkoxy, alkenyloxy, aryloxy, carboxy, benzyloxy, haloalkoxy, haloalkenyloxy, haloaryloxy, nitro, nitroalkyl, nitroalkenyl, nitroalkynyl, nitroaryl, nitroheterocyclyl, azido, amino, alkylamino, alkenylamino, alkynylamino, arylamino, benzylamino, acylamino, acyl, alkenylacyl, alkynylacyl, arylacyl, acylamino, acyloxy, aldehydo, alkylsulphonyl, arylsulphonyl, sulphonylamino, alkylsulphonylamino, arylsulphonylamino, alkylsulphonyloxy, arylsulphonyloxy, heterocyclyl, heterocycloxy, heterocyclylamino, haloheterocyclyl, alkylsulphenyl, arylsulphenyl, carboalkoxy, carboaryloxy, mercapto, sulfonic acid, alkylthio, arylthio and acylthio.

The term "halo" denotes fluorine, chlorine, bromine or iodine.

Specific examples of the betaine compound include, for example, the following betaine compounds:

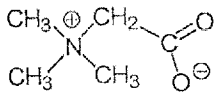
Betaine compound	**Other names**
glycine betaine	Oxynurine
β-alaninebetaine	Homobetaine
prolinebetaine	Stachydrine
(-)-4-hydroxy prolinebetaine	Betonicine
(+)-4-hydroxy prolinebetaine	Turicine
3-hydroxyprolinebetaine	3-Oxystachydrine
histidinebetaine	Herzynine, Ercinine
tryptophanbetaine	Hypaphorine
2-mercaptohistidinebetaine	Ergothioneine
pipecolatebetaine	Homostachydrine
nicotinic acid betaine	Trigonelline
3-dimethylsulfoniopropionate (DMSP)	
choline-O-sulfate	
$(CH_3)_3P^+CH_2S(=O)_2O^-$	

In preferred embodiments, the compound of the invention administered is N-methyl-L-proline, *trans*-4-hydroxy-N-methyl-L-proline, (-)-4-hydroxy prolinebetaine

(Betonicine), (+)-4-hydroxy prolinebetaine (Turicine) or nicotinic acid betaine (Trigonelline).

The betaine compound may be obtained from plants such as sugar beet, *Melaleuca species* or *Eucalyptus* species, any microorganisms (eg. yeast, bacteria and fungi), or may be artificially synthesised.

In a preferred embodiment, the betaine compound is glycine betaine having the following formula:



The therapeutically effective amount of the compound of the invention may be administered to the subject in a single daily dose, or in several doses throughout a day, during a course of treatment. Typically, the compound of the invention is administered at regular intervals over a course of treatment. For example, the compound of the invention may be administered as a single daily dose throughout the course of treatment. The course of treatment may last for any length of time as required by the subject, e.g. one day, several days, several weeks, several months, or several years, to have the desired therapeutic effect.

The lowering of blood-glucose levels may be observed within days to weeks or months after commencing administration of the compound of the invention. It may be desirable for some subjects who have succeeded in attaining healthy blood-glucose levels to continue the administration of the compound of the invention indefinitely, in lower doses if necessary, to maintain healthy blood-glucose levels.

The administration of a compound of the invention in conjunction with an antihyperlipidemic agent may enhance the antihyperlipidemic activity of the antihyperlipidemic agent. That is, a further decrease in blood-lipid levels may be observed when a compound of the invention is administered in conjunction with an antihyperlipidemic agent.

Thus, in another aspect, the present invention provides a method of enhancing the activity of an antihyperlipidemic agent in a human or animal subject being treated with the antihyperlipidemic agent, the method comprising administering to the subject a therapeutically effective amount of a compound of the invention.

In a further aspect, the present invention provides the use of a compound of the invention in the manufacture of a medicament for enhancing the activity of an antihyperlipidemic agent in a human or animal subject being treated with the antihyperlipidemic agent.

The following are examples of antihyperlipidemic agents which are currently available for use in Australia:

- **Statins**. The statins are a class of antihyperlipidemic agents including: atorvastatin (brand name Lipitor), fluvastatin (Lescol or Vastin), pravastatin (Pravachol), and simvastatin (Lipex or Zocor). The statins are sometimes referred to as inhibitors of HMG CoA reductase which is an enzyme in the biosynthesis of cholesterol.
- **Ezetimibe**. Ezetimibe (brand name Ezetrol) is an antihyperlipidemic agent which inhibits cholesterol absorption. Ezetimibe reduces total cholesterol, LDL and triglycerides, and increases HDL cholesterol.
- **Cholestyramine and colestipol**. Cholestyramine (brand name Questran Lite) and colestipol (Colestid granules) bind to bile acids in the intestine, preventing them from being reabsorbed into the body and thereby releasing the bile acids through the faeces. To make more bile acids, the body needs cholesterol. This results in a higher demand for cholesterol by the body, and this demand for cholesterol plays a role in reducing the blood level of cholesterol.
- **Gemfibrozil and fenofibrate.** Gemfibrozil (brand name Lopid) is a lipid-lowering medication. Gemfibrozil is used if high triglycerides predominate as opposed to other lipids. Fenofibrate (Lipidil) is a new alternative medication to gemfibrozil for the treatment of high triglycerides.

- **Nicotinic acid**. Nicotinic acid can lower LDL cholesterol and triglycerides and also increases HDL cholesterol. Nicotinic acid is often used where the lipid that is predominantly elevated is triglyceride.
- **Fish oil**. Omega-3 containing fish oil is used for lowering triglycerides without side effects.
- **Plant sterols**. Plant sterols reduce cholesterol without any side effects.

The therapeutically effective amount of the compound of the invention may depend on the following factors:

(a) the particular compound of the invention used,
(b) the characteristics of the subject being treated (risk factors such as family history, lifestyle, age, ethnic origin, diet),
(c) the severity and type of the affliction, and
(d) the manner of administration of the compound of the invention.

The therapeutically effective amount may be determined by various methods, including the following:

(1) generating an empirical dose-response curve,
(2) predicting potency and efficacy by using quantitative structure activity relationships (QSAR) methods,
(3) molecular modelling, and
(4) other methods used in the pharmaceutical sciences.

For an adult human subject, the therapeutically effective amount may be in the range of from about 500 to about 50,000 mg per day, e.g. 1,000 to 50,000 mg per day. In one embodiment, the therapeutically effective amount is or is at least about 1,000 mg per day. In another embodiment, the therapeutically effective amount is or is at least about 2,000 mg per day. In another embodiment, the therapeutically effective amount is or is at least about 50,000 mg per day. The total daily dose of the compound of the invention may be administered to the subject in divided doses to be taken at various intervals throughout the day, e.g. 1,000 to 5,000 mg twice a day or thrice a day.

In some embodiments, two or more different compounds of the invention are administered to the subject. In some embodiments, the compound of the invention is administered to the human or animal subject in the absence of the administration of any other pharmaceutically active agents. In some embodiments, the compound of the invention is administered in combination with one or more other pharmaceutically active agents, such as one or more antidiabetic agents or one or more antihyperlipidemic agents. The compound of the invention and the antidiabetic agent or antihyperlipidemic agent may be administered together or separately.

The antidiabetic agent may be, for example, selected from the following classes:

1) **Sulfonylureas** (e.g. chlorpropamide [brand name Diabinese], tolazamide [Tolinase], glipizide [Glucotrol] and others). Sulfonylureas act by increasing insulin release from the beta cells of the pancreas. Glimepiride (Amaryl), a member of this class, appears to have a useful secondary action in increasing insulin sensitivity in peripheral cells.

2) **Alpha-glucosidase inhibitors** (e.g. acarbose [brand name Precose], miglitol [Glyset]). Alpha-glucosidase inhibitors do not enhance insulin secretion. Rather, they inhibit the conversion of disaccharides and complex carbohydrates to glucose. This mechanism does not prevent conversion, but only delays it, reducing the peak blood-glucose levels.

3) **Biguanides**. Metformin (brand name Glucophage) is the only currently available member of the biguanide class. Metformin decreases hepatic (liver) glucose production, decreases intestinal absorption of glucose and increases peripheral glucose uptake and use.

4) **Meglitinides** (e.g. repaglinide [brand name Prandin] and nateglitinide [Starlix]). The mechanism of action of the meglitinides is to stimulate insulin production.

5) **Thiazolidinediones** (e.g. rosiglitazone [brand name Avandia] and pioglitazone [Actos]). Thiazolidinediones act by reducing glucose production in the liver and increasing insulin dependent glucose uptake in muscle cells. They do not increase insulin production.

The antihyperlipidemic agent may be, for example, selected from the examples of antihyperlipidemic agents referred to above.

The compound of the invention may be administered to the human or animal subject in the form of a composition comprising the compound of the invention and a pharmaceutically acceptable carrier. The compound of the invention is typically administered in the form of a composition comprising the compound of the invention together with a pharmaceutically acceptable carrier. In some embodiments, the composition comprises two or more compounds of the invention.

In some embodiments, the composition is formulated as an extended-release or controlled-release formulation, to enable slow- or controlled-release of the compound of the invention into the subject's body. In a preferred embodiment, the extended-release or controlled-release formulation comprises glycine betaine, which, on administration, enables slow- or controlled-release of glycine betaine into the subject's body.

One or more of the following known extended- or controlled-release mechanisms can, for example, be used to deliver the compound of the invention into the subject's body (Lonsdale HK, "Review: The Growth of Membrane Technology", *J. Memb. Sci.*, **10**, 81-181 (1982)):

- the compound of the invention may be contained in a polymer matrix of a film (monolithic device);
- the compound of the invention may be contained by a polymer (reservoir device);
- the compound of the invention may be mixed with polymeric colloidal particles or microencapsulates (microparticles, microspheres or nanoparticles) in the form of reservoir and matrix devices;

- the compound of the invention may be contained in a polymer containing a hydrophilic and/or leachable additive, e.g. a second polymer, surfactant or plasticiser, etc., to give a porous device, or a device in which the release of the compound of the invention may be osmotically 'controlled' (both reservoir and matrix devices);
- the compound of the invention may be housed in an enteric coating which ionises and dissolves at a suitable pH in the subject's body;
- the compound of the invention may be covalently attached (as a "pendant" molecules) to soluble polymers;
- the compound of the invention may be delivered by a devices where the rate of release of the compound of the invention is controlled dynamically, e.g. by an osmotic pump.

In preferred embodiments, the extended- or controlled-release formulation containing the compound of the invention is a tablet comprising a polymer matrix such as methyl cellulose.

In some embodiments, the composition does not contain any pharmaceutically active agents in addition to the compound of the invention. In other embodiments, the composition further comprises one or more pharmaceutically active ingredients in addition to the compound of the invention, e.g. one or more antidiabetic agents selected from the classes of antidiabetic agents described above, or one or more antihyperlipidemic agents selected from the antihyperlipidemic agents described above.

As used herein, a "pharmaceutically acceptable carrier" is a pharmaceutically acceptable solvent, suspending agent or vehicle for delivering the compound of the invention to a human or animal subject. The carrier may be liquid or solid and is selected with the planned manner of administration in mind. The carrier is "pharmaceutically acceptable" in the sense of being not biologically or otherwise undesirable, i.e. the carrier may be administered to a human or animal subject along with the compound of the invention without causing any or a substantial adverse reaction.

The composition may be administered by any means that achieve the intended purpose of lowering blood-glucose levels. For example, the composition may be administered to a subject through systemic administration, e.g. oral, rectal (by suppository), parenteral (including subcutaneous, intramuscular, intraperitoneal, intralesional, intravenous and intradermal), topical, nasal, buccal, sublingual, ophthalmological and vaginal administration for the treatment. For example, compositions in the form of parenteral formulations usually comprise injectable fluids that include pharmaceutically and physiologically acceptable fluids such as water, physiological saline, balanced salt solutions, aqueous dextrose, glycerol or the like as a vehicle. For solid compositions (e.g. powder, pill, tablet or capsule forms), conventional non-toxic solid carriers may include, for example, pharmaceutical grades of mannitol, lactose, starch, or magnesium stearate. In addition to biologically-neutral carriers, pharmaceutical compositions to be administered can contain minor amounts of non-toxic auxiliary substances, such as wetting or emulsifying agents, preservatives, and pH buffering agents and the like, for example sodium acetate or sorbitan monolaurate.

In addition to administering the composition, other measures may be taken to prevent or treat hyperglycemia in the subject. Risk factors for hyperglycemia include family history, lifestyle, age, ethnic origin and diet. For example, in some embodiments, a subject may be instructed, trained, or induced to adopt, antidiabetic lifestyle modifications such as suitable diet and exercise.

The composition may conveniently be presented in unit dosage form and may be prepared by methods well known in the art of pharmacy. Such methods include the step of bringing into association the compound(s) of the invention with the carrier. Typically, the carrier comprises two or more ingredients. In general, the composition of the present invention is prepared by uniformly and intimately bringing into association the compound of the invention with the carrier, and then, if necessary, shaping the product. Typically, the compound of the invention and the one or more ingredients making up the carrier may be mixed in any order.

A composition for oral administration may be in the form of a tablet, a capsule, a paste, a chewable formulation, or any other form suitable for oral administration. If desired,

the composition may be encapsulated in a soft or hard capsule by techniques known in the art.

A composition for oral use may comprise one or more agents selected from the group of sweetening agents, disintegrates, flavouring agents, colouring agents and preserving agents in order to produce pharmaceutically elegant and palatable preparations.

The subject may be any human or animal in need of prevention or treatment of hyperglycemia. The subject may be a human or animal having hyperglycemia, or may be a subject at risk of developing hyperglycemia. The subject may have diabetes (type 1, type 2 or gestational diabetes) or be at risk of developing diabetes (type 1, type 2 or gestational diabetes).

The animal may, for example, be a companion animal such as a dog or cat, or a domestic animal such as a horse, pony, donkey, mule, llama, alpaca, pig, cow or sheep, or a zoo animal.

Suitable animals include members of the Orders *Primates, Rodentia, Lagomorpha, Cetacea, Carnivora, Perissodactyla* and *Artiodactyla*.

The invention is described below by reference to the following non-limiting Examples. It will be appreciated by persons skilled in the art that numerous variations and/or modifications may be made to the invention as shown in the following Examples without departing from the spirit or scope of the invention as broadly described. The Examples are, therefore, to be considered in all respects as illustrative and not restrictive.

EXAMPLES

Example 1

This experiment studies the effect of glycine betaine on a 44 year old Indian male human with a history of hyperglycemia (type 2 diabetes) and hyperlipidemia. For four

years preceding this experiment, the subject was taking Metformin (metformin hydrochloride) (500 mg twice daily) and Lipitor (atorvastatin calcium) (1x10 mg daily).

Before the experiment, the average of morning fasting blood-glucose levels of the subject taking 2x500 mg of Metformin (metformin hydrochloride) per day was 8.3 mmol. The total blood-lipid level of the subject taking 1x10 mg of Lipitor (atorvastatin calcium) per day was 7.1 mmol. There was no significant change in lifestyle (physical activity or diet) for this subject during the period of the experiment.

Oral administration of glycine betaine (3x3,000 mg per day), in addition to the intake of Metformin and Lipitor, was commenced in April. Two months later in June, the subject discontinued taking Metformin and Lipitor, and continued the administration of glycine betaine. The subject's morning fasting blood-glucose levels were measured over the following 7 days. Blood samples were analysed by Queensland Medical Laboratories (QML) to determine fasting blood-glucose and blood-lipid levels (see Table 1 below).

Table 1: Effect of glycine betaine on blood chemistry and body weight of subject

	Month of blood test		
	Dec '03	April '04	June '04
Treatment parameter	Metformin and Lipitor only (prior to glycine betaine intake)	Metformin, Lipitor and glycine betaine since Dec '03	Glycine betaine only; Metformin and Lipitor discontinued since April '04
Blood-glucose (mmol)	8.3	6.5	6.9
Total blood-lipid (mmol)	7.1	4.9	8.2

The subject's body weight reduced significantly since the commencement of administering glycine betaine by more than one kilogram per month. Further, since the commencement of administering glycine betaine, blood-glucose levels were found to have decreased from 8.3 to 6.5 mmol (22% reduction) (see Table 1). A similar effect was observed in the total blood-lipid levels which decreased from 7.1 (maintained with

Metformin and Lipitor only) to 4.9 mmol with Metformin, Lipitor and glycine betaine (31% reduction). After discontinuation of Metformin and Lipitor, and during the period when only glycine betaine was taken, the subject's blood-glucose levels were maintained at levels similar to the levels when Metformin, Lipitor and glycine betaine were being taken, which was approximately 17% lower than the blood-glucose levels when only Metformin and Lipitor were being taken.

This data shows that glycine betaine itself exhibits blood-glucose lowering ability, and also improves the action of Metformin. This data also shows that glycine betaine improves the lipid-lowering action of Lipitor.

Example 2

Mice strain C57BL/6J has been specially bred for their ability to develop obesity-induced type 2 diabetes and high lipid levels. This is a well-known and accepted model of obesity-induced physiological disorders in humans (Opara EC, Petro A, Tevrizian A, Feinglos MN, and Surwit RS, "L-glutamine supplementation of a high fat diet reduces body weight and attenuates hyperglycemia and hyperinsulinemia in C57BL/6J mice". *Journal of Nutrition*, **126**: 273-279 (1996)).

The following experiment was conducted to confirm the effects of glycine betaine observed in Example 1 above on blood-glucose levels, blood-lipid levels and body weight using a mice model.

All the procedures described in this experiment were approved by the animal ethics committee of the Department of Primary Industries and Fisheries in Queensland State of Australia.

MATERIALS AND METHODS: Twenty male and twenty female mice, seven weeks of age, were purchased from the University of Queensland. Individual mice were housed in separate cages of 42 x 25 x 10cm with wire tops, with a floor space of 1050 cm^2. Natty cat litter (2 cm depth) was used as bedding and was changed weekly. Water was supplied via bottle and drinker nipple. Lighting was standard fluorescent

tubes on timers (12 hours on/off). The room was heated to maintain a minimum temperature of 22°C. A high fat-containing dairy-based basal diet was prepared (Tables 2 and 3) based on Nishina PM, Wang J, Toyofuku W, Kuypers FA, Ishida BY, Paigen B, "Atherosclerosis and plasma and liver lipids in nine inbred strains of mice". *Lipids*. **28**: 599-605 (1993). All mice were fed the basal diet for the first week to acclimatise the mice to the new diet and new environment.

Table 2: Ingredients of the basal diet

	Wt (g)	% (w/w)
Cheese (mature cheddar cheese with 26% protein, 33% fat and about 40% moisture, produced by Black and Gold, Australia)	780	63.2
Sucrose	300	24.3
Cornflour	150	12.2
Minerals & Vitamins (Avi-vit by Aristopet, Australia)	4	0.3
Total fresh weight	**1234**	**100.0**

Table 3: Total energy content (kcal/1234 g fresh weight) of the diet

	kcal	% Contribution
Carbohydrates	1800.0	36.5
Protein	811.2	16.4
Fat	2316.6	46.9
Vitamins	8.0	0.2
Minerals	0.0	0.0
Total	**4935.8**	100.0

The basal diet was supplemented with 0.00, 0.25, 0.50, and 1.00% w/w glycine betaine obtained from FinnFoods, Finland. The differences in energy of various treatment feeds (due to the variation of glycine betaine) were adjusted by adding 1.00, 0.75, 0.5, and 0.00% w/w glycine to the treatments 1, 2, 3, and 4, respectively.

After the acclimatisation period, when the mice were eight weeks old, the mice were randomly assigned to the following four treatments with four replications.

Treatment 1 (control):	0.00% added glycine betaine
Treatment 2:	0.25% added glycine betaine
Treatment 3:	0.50% added glycine betaine
Treatment 4:	1.00% added glycine betaine

In each treatment, mice were fed with various treatmental diets ad-lib for 8 weeks (i.e. mice were sixteen weeks old when the experiment was concluded). The mice were allowed unrestricted access to the feed. The weights of individual mice were recorded by placing the mouse in a container on an electronic scale accurate to 0.1 g. Feed intake was monitored from the difference in the weights of added and unconsumed diet. At fortnightly intervals, after overnight feed withdrawal/fasting, 1 drop of blood was collected from the lateral tail vein of each mouse for monitoring blood-glucose levels using a glucose meter, Advantage, using Accucheck Advantage II test strips. A second drop of blood was collected, at the same time, to measure total lipid using Accutrend GC meter with Accutrend lipid strips. The glucose and lipid meters, and the test strips were made by Roche.

RESULTS: Feed intake of both male and female mice increased significantly from the beginning of the experiment up to four weeks and then stayed almost constant for the remaining four-week period (Fig. 1). Male mice consumed more feed compared to female mice. However, no differences were found in feed intake due to the glycine betaine content of the diet.

Weight gain of mice almost reflected their feed intake. Male mice attained greater final weight compared to the female mice (Fig. 2). Most interestingly, at four weeks after glycine betaine supplementation, at 0.5 and 1% levels, both male and female mice showed significantly less weight gain compared to the control mice. This difference was maintained for a further period of 4 weeks at the end of the experiment only at 1% of betaine supplementation. During the eight-week period, male mice grew from the initial weight of 20.1 g to the final weights of 32.4 g and 28.7 g in control and glycine

betaine-supplemented groups, respectively. This represents 61% and 43% weight gain in control and glycine betaine groups, respectively. Glycine betaine-supplemented male mice were 11% lighter than controls. During the corresponding period, the female mice grew from the initial weight of 16.4 g to the final weights of 24.4 g and 20.5 g in control and glycine betaine-supplemented groups, respectively. This represents 49% and 25% weight gain in control and glycine betaine treatments, respectively. Glycine betaine-supplemented female mice were 16% lighter than controls.

Male and female mice developed moderate and slight level of diabetes, respectively, in the eight-week experimental period by showing fasting blood-glucose level of 8.2 mmol and 6.7 mmol, respectively (Fig. 3). Most interestingly, in the male mice, glycine betaine supplementation resulted in a significant reduction in diabetes evidenced with a blood-glucose level of 6.4 mmol; in the female mice, diabetes was completely prevented with a blood-glucose level of only 5.2 mmol. In both sexes, intake of glycine betaine reduced blood-glucose levels by about 22% compared to the control group. This decrease in the blood-glucose levels of both female and male mice on glycine betaine-supplemented diets appeared from two weeks after the treatment had begun (Fig. 3). For both cases, these differences became significant in 0.5 and 1% glycine betaine-supplemented treatments at four and six weeks after treatment had begun, respectively.

Total cholesterol levels in the mice blood samples were below the detection limit (about 3.5 mmol) of the Accutrend GC meter, suggesting that the development of hyperlipidemia may take longer than the current experimental period.

In Figures 1, 2 and 3, time 0 is the time at which the mice were separated into four groups and feed with the various treatmental diets commenced.

Discussion

Examples 1 and 2 described above show that an intake of about 9 g betaine/day in humans and the incorporation of about 0.5% w/w of glycine betaine in the diet of mice lead to a reduction of body weight and presumably body fat. The addition of glycine betaine to the diet has been shown to result in reduced blood-glucose levels.

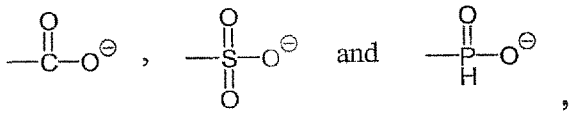
It is to be understood that a reference herein to a prior art document does not constitute an admission that the document forms part of the common general knowledge in the art in Australia or in any other country.

In the claims which follow and in the preceding description of the invention, except where the context requires otherwise due to express language or necessary implication, the word "comprise" or variations such as "comprises" or "comprising" is used in an inclusive sense, i.e. to specify the presence of the stated features but not to preclude the presence or addition of further features in various embodiments of the invention.

CLAIMS

1. A method of preventing or treating hyperglycemia in a human or animal subject, the method comprising administering to the subject a therapeutically effective amount of a compound selected from the group consisting of:

(a) a betaine compound having a positively-charged group selected from group consisting of a quaternary ammonium group, a quaternary phosphonium group and a tertiary sulfonium group, and a negatively-charged group selected from the group consisting of:



(b) 2-trimethylamino-6-ketoheptanoate,

(c) proline,

(d) N-methyl-L-proline, *trans*-4-hydroxy-N-methyl-L-proline,

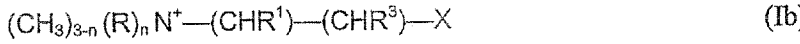
(e) *cis*-3-hydroxy-N-methyl-L-proline, and

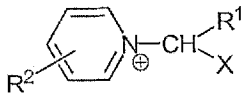
(f) choline.

2. The method according to claim 1, wherein the compound is selected from the group consisting of:

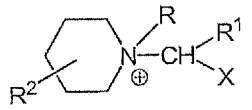
 (I)

 (Ia)

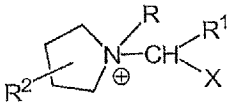
 (Ib)



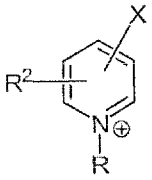
(II)



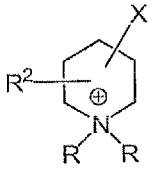
(III)



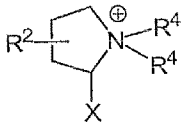
(IV)



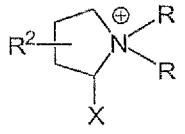
(V)



(VI)



(VII)



(VIIa)

wherein n is 0, 1 or 2;

m is 1 or 2;

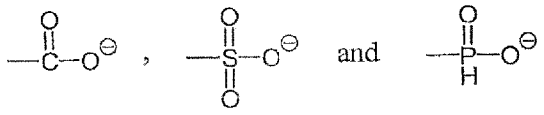
R is selected from the group consisting of optionally substituted alkyl and optionally substituted aryl groups;

R^1 and R^3 are independently selected from the group consisting of H, optionally substituted alkyl groups, carboxyl and side chains of amino acids;

R^2 is selected from the group consisting of OH, halo, optionally substituted alkyl groups, NH_2 and electrophilic groups;

R^4 is an optionally substituted alkyl group; and

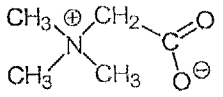
X is selected from the group consisting of



3. The method according to claim 1, wherein the compound is selected from the group consisting of: glycine betaine, β-alaninebetaine, 2-trimethylamino-6-ketoheptanoate, prolinebetaine, proline, N-methyl-L-proline, *trans*-4-hydroxy-N-methyl-L-proline, *cis*-3-hydroxy-N-methyl-L-proline, (-)-4-hydroxy prolinebetaine, (+)-4-hydroxy prolinebetaine, 3-hydroxyprolinebetaine, histidinebetaine, tryptophanbetaine, 2-mercaptohistidinebetaine, pipecolatebetaine, nicotinic acid betaine, 3-dimethylsulfoniopropionate (DMSP), choline-O-sulfate, choline and $(CH_3)_3P^+CH_2S(=O)_2O^-$.

4. The method according to claim 3, wherein the compound is selected from the group consisting of N-methyl-L-proline, *trans*-4-hydroxy-N-methyl-L-proline, (-)-4-hydroxy prolinebetaine (Betonicine), (+)-4-hydroxy prolinebetaine (Turicine) and nicotinic acid betaine (Trigonelline).

5. The method according to claim 3, wherein the compound is glycine betaine having the following formula:



6. The method according to any one of claims 1 to 5, wherein a total of at least about 30 mg/kg body weight of the compound is administered to the subject per day.

7. The method according to claim 6, wherein a total of from about 20 mg/kg body weight to about 400 mg/kg body weight of the compound is administered to the subject per day.

8. The method according to claim 7, wherein a total of from about 100 mg/kg body weight to about 400 mg/kg body weight of the compound is administered to the subject per day.

9. The method according to any one of claims 6 to 8, wherein the total daily amount of the compound is administered to the subject in a single daily dose.

10. The method according to any one of claims 1 to 9, wherein the compound is administered in combination with an antidiabetic agent.

11. The method according to claim 10, wherein the antidiabetic agent is selected from the group consisting of sulfonylureas, alpha-glucosidase inhibitors, biguanides, meglitinides and thiazolidinediones.

12. The method according to claim 11, wherein the antidiabetic agent is the biguanide Metformin.

13. The method according to any one of claims 1 to 12, wherein the compound is administered in the form of a composition comprising the compound and a pharmaceutically acceptable carrier.

14. The method according to claim 13, wherein the composition further comprises an antidiabetic agent.

15. The method according to claim 14, wherein the antidiabetic agent is selected from the group consisting of sulfonylureas, alpha-glucosidase inhibitors, biguanides, meglitinides and thiazolidinediones.

16. The method according to claim 15, wherein the antidiabetic agent is the biguanide metformin.

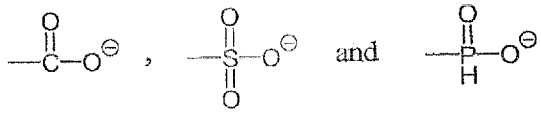
17. The method according to any one of claims 13 to 16, wherein the composition is an extended-release or controlled-release formulation.

18. The method according to any one of claims 13 to 16, wherein the composition is in the form of an injectable liquid or a solid.

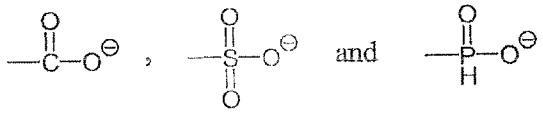
19. The method according to any one of claims 1 to 18, wherein the subject has diabetes.

20. The method according to any one of claims 1 to 19, wherein the subject is human.

21. Use of a compound selected from the group consisting of:



(a) a betaine compound having a positively-charged group selected from group consisting of a quaternary ammonium group, a quaternary phosphonium group and a tertiary sulfonium group, and a negatively-charged group selected from the group consisting of:



(b) 2-trimethylamino-6-ketoheptanoate,

(c) proline,

(d) N-methyl-L-proline, *trans*-4-hydroxy-N-methyl-L-proline,

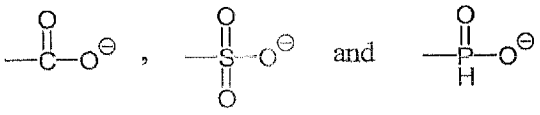
(e) *cis*-3-hydroxy-N-methyl-L-proline, and

(f) choline,

in the manufacture of a medicament for preventing or treating hyperglycemia.

22. A method of enhancing the activity of an antihyperlipidemic agent in a human or animal subject being treated with the antihyperlipidemic agent, the method comprising administering to the subject a therapeutically effective amount of a compound selected from the group consisting of:

(a) a betaine compound having a positively-charged group selected from group consisting of a quaternary ammonium group, a quaternary phosphonium group and a tertiary sulfonium group, and a negatively-charged group selected from the group consisting of:



(b) 2-trimethylamino-6-ketoheptanoate,

(c) proline,

(d) N-methyl-L-proline, *trans*-4-hydroxy-N-methyl-L-proline,

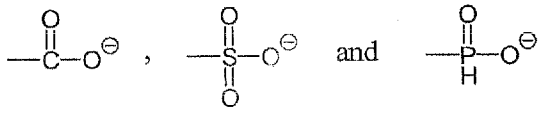
(e) *cis*-3-hydroxy-N-methyl-L-proline, and

(f) choline.

23. The method according to claim 22, wherein the antihyperlipidemic agent is selected from the group consisting of a statin compound, ezetimibe, cholestyramine, colestipol, gemfibrozil, fenofibrate, nicotinic acid, fish oil and a plant sterol.

24. The use of a compound selected from the group consisting of:

(a) a betaine compound having a positively-charged group selected from group consisting of a quaternary ammonium group, a quaternary phosphonium group and a tertiary sulfonium group, and a negatively-charged group selected from the group consisting of:



(b) 2-trimethylamino-6-ketoheptanoate,

(c) proline,

(d) N-methyl-L-proline, *trans*-4-hydroxy-N-methyl-L-proline,

(e) *cis*-3-hydroxy-N-methyl-L-proline, and

(f) choline,

in the manufacture of a medicament for enhancing the activity of an antihyperlipidemic agent in a human or animal subject being treated with the antihyperlipidemic agent.

Figure 1

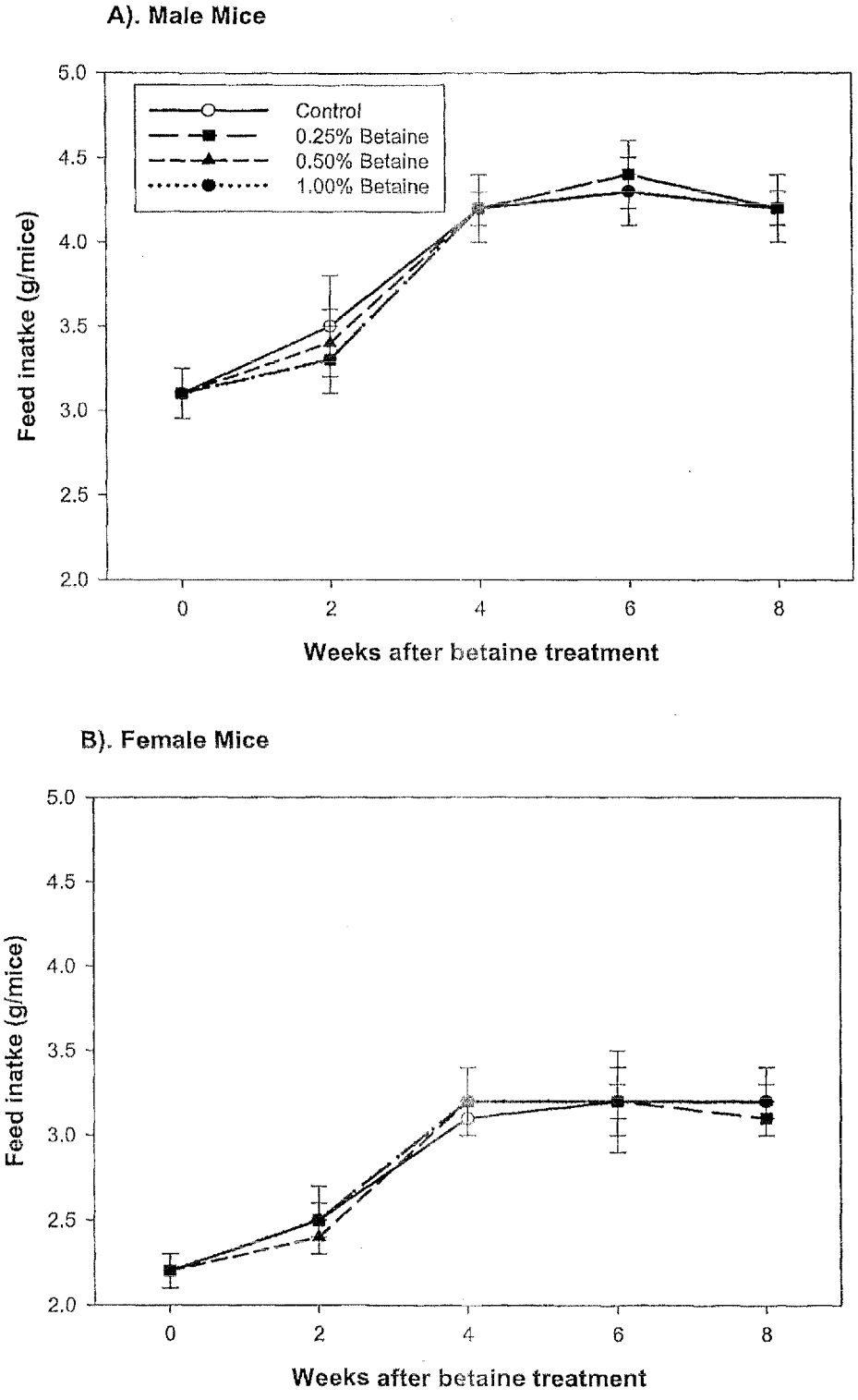

A). Male Mice
Control
0.25% Betaine
0.50% Betaine
1.00% Betaine
Feed inatke (g/mice)
5.0
4.5
4.0
3.5
3.0
2.5
2.0
0
2
4
6
8
Weeks after betaine treatment
B). Female Mice
Feed inatke (g/mice)
5.0
4.5
4.0
3.5
3.0
2.5
2.0
0
2
4
6
8
Weeks after betaine treatment

Figure 2

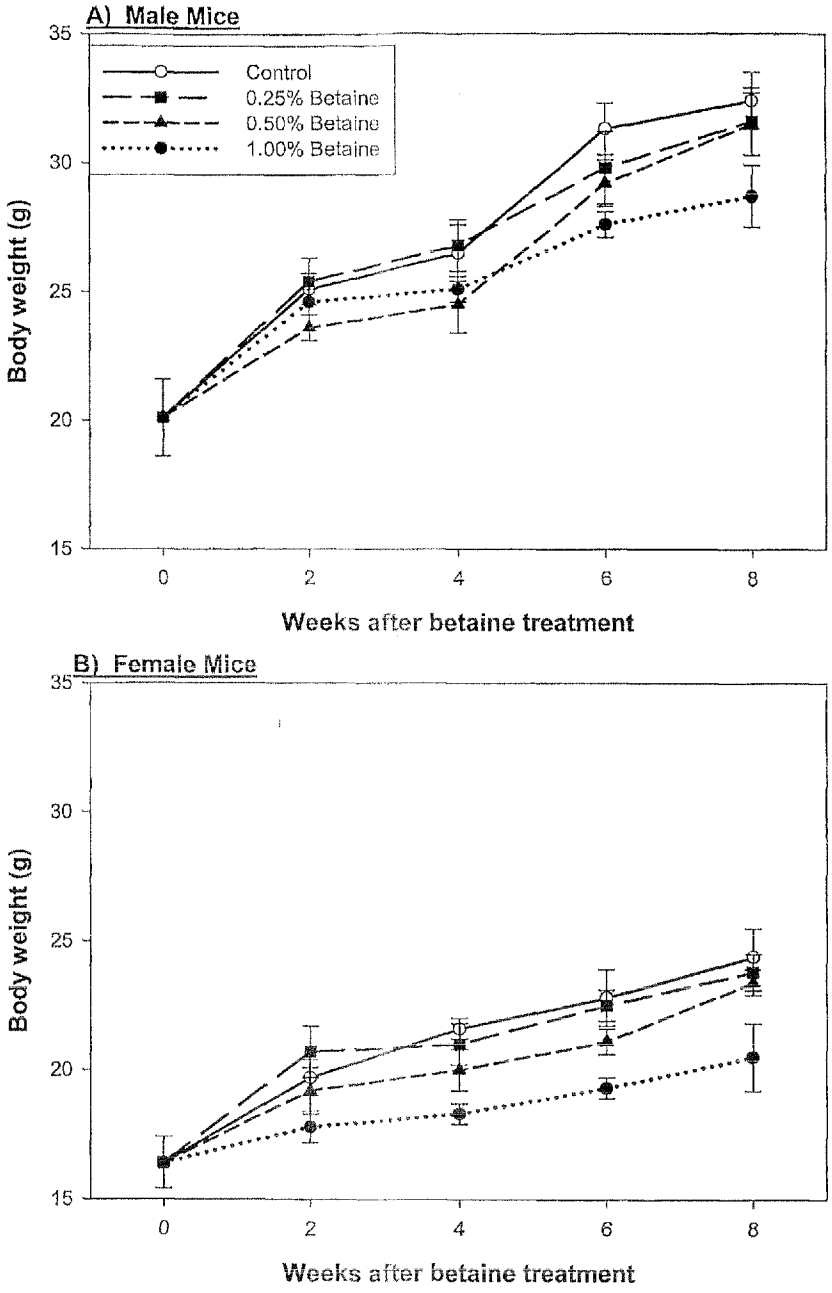
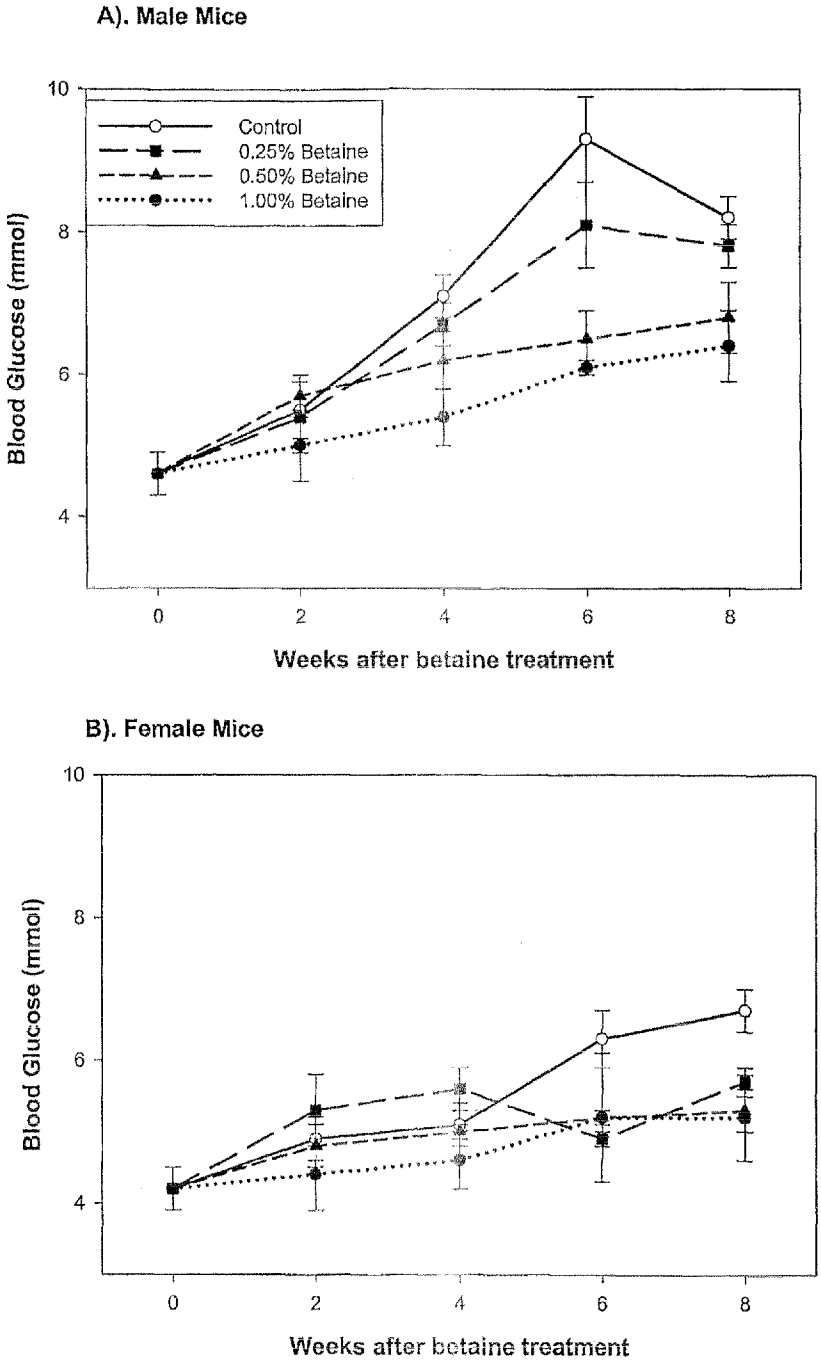

A) Male Mice
Control
0.25% Betaine
0.50% Betaine
1.00% Betaine
Body weight (g)
35
30
25
20
15
0
2
4
6
8
Weeks after betaine treatment
B) Female Mice
Body weight (g)
35
30
25
20
15
0
2
4
6
8
Weeks after betaine treatment

Figure 3


A). Male Mice
Control
0.25% Betaine
0.50% Betaine
1.00% Betaine
Blood Glucose (mmol)
Weeks after betaine treatment
B). Female Mice
Blood Glucose (mmol)
Weeks after betaine treatment

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU2005/000014

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl. [7]: A61K 31/205, 31/14, 31/401, A61P 3/06, 3/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
WPIL, MEDLINE, JAPIO; keywords-diabetes, hyperglycemia, hyperlipidemia, betaine, proline, choline.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 080695 B1 (Takeda Chemical Industries, Ltd) 17 April 1985. Whole document.	1-24
X	JP 2003-261445 A (Nippon Beet Sugar Mfg Co Ltd) 16 September 2003. English Language Abstract.	22-24
X	JP 08-133970 A (Nippon Beet Sugar Mfg Co Ltd) 28 May 1996. English Language Abstract.	1-3, 21-24
X,P	JP 2004-091475 A (Taisho Pharmaceut Co Ltd) 25 March 2004. English Language Abstract.	22-24

[X] Further documents are listed in the continuation of Box C [X] See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 February 2005	03 MAR 2005
Name and mailing address of the ISA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	Authorized officer G.R.PETERS Telephone No : (02) 6283 2184

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU2005/000014

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X, P	WO 2004/100968 A (Indus Biotech Pvt, Ltd) 25 November 2004. Whole document.	1-21

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU2005/000014

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. Claims 1-21 that define methods for treating hyperglycemia in a human or animal subject and the use of certain compounds for producing a medicament therefore.

2. Claims 22-23 that define methods for enhancing the activity of an antihyperlipidemic agent in a human or animal subject and the use of certain compounds for producing a medicament therefore.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☒ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/AU2005/000014

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report	Patent Family Member					
EP 080695	CA	1190166	JP	58096049	US	4521432
	US	4767781	WO	1984/001574		

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

END OF ANNEX